Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

Certificate of Mailing
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop: Appeal Briefs-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on January 5, 2004.
By: _____ Printed: Lyza Finuliar

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Bandman et al.

Title:	NOVEL HUMAN SELENIUM-BINDING PROTEIN		
Serial No.:	09/841,758	Filing Date:	April 24, 2001
Examiner:	Yaen, C.	Group Art Unit:	1642

Mail Stop Appeal Briefs-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF ON APPEAL

Sir:

This is Appellants' Reply Brief On Appeal (submitted in triplicate) in response to the Examiner's Answer dated November 5, 2003 ("the Examiner's Answer") in the above-identified application.

In the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of Claims 1, 2, 13, and 14 under 35 U.S.C. § 101 on the grounds that the claimed polypeptide allegedly does not possess a specific asserted utility or a well established utility;

(2) maintained the rejection of Claims 1, 2, 13, and 14 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement because of the invention's alleged lack of utility; and

(3) maintained the rejection of Claims 1, 2, 13, and 14 under 35 U.S.C. § 112, first paragraph for alleged lack of written description of the claimed polypeptide variants and fragments.

I. UTILITY REJECTION OF CLAIMS 1, 2, 13, AND 14

A. Submission of Declarations

The Examiner's Answer is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the priority Bandman '903 application relating to the use of the SEQ ID NO:1 polypeptide for gene and protein expression monitoring applications. Such gene and protein expression monitoring applications are highly useful in drug development and in toxicity testing.

The Examiner's new positions and arguments include that (a) the Specification allegedly does not disclose toxicology testing (Examiner's Answer, page 21) and (b) the gene and protein expression monitoring results obtained using the SEQ ID NO:1 polypeptide are allegedly "meaningless" and "useless" or otherwise insufficient to constitute substantial, specific and credible utilities for the SEQ ID NO:1 polypeptide (Examiner's Answer, e.g., page 17-23).

Under the circumstances, Appellants are submitting with this Reply Brief (in triplicate) Declarations under 37 C.F.R. § 1.132 of John C. Rockett, Ph.D. (hereinafter the "Rockett Declaration"), of Tod Bedilion, Ph.D. (hereinafter "the Bedilion Declaration"), and of Vishwanath R. Iyer, Ph.D. (hereinafter the "Iyer Declaration"), and seven (7) references published before or shortly after the November 15, 1996 filing date of the priority Bandman '903 application. As we will show, the Rockett Declaration, the Bedilion Declaration, the Iyer Declaration, and the accompanying references show the many substantial reasons why the Examiner's new positions and arguments with respect to the use of the SEQ ID NO:1 polypeptide in gene and protein expression monitoring applications are without merit.

The fact that the Rockett Declaration, the Bedilion Declaration, the Iyer Declaration, and the accompanying references are being submitted in response to positions taken and arguments made for the first time in the Examiner's Answer, constitutes, by itself, "good and sufficient reasons" under 37 C.F.R. § 1.195 why those Declarations were not earlier submitted and should be admitted at this time. Appellants also note that the submitted Declarations and references are responsive to the new utility rejection as framed by the Board of Appeals in copending cases with similar issues.

B. Utility of the Claimed Polypeptide in Toxicology Testing

The Examiner's Answer asserts that the utilities of the claimed polypeptides in expression profiling and toxicology testing would allegedly not have been recognized by one of

skill in the art as well-established at the time of filing (Examiner's Answer, page 21). Appellants submit three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and seven (7) scientific references published before or shortly after the November 15, 1996 priority date of the instant application. The previously submitted Furness Declaration, as well as the currently submitted Rockett Declaration, Bedilion Declaration, and the Iyer Declaration, and the seven (7) references fully establish that, prior to the November 15, 1996 filing date of the priority Bandman '903 application, it was well-established in the art that:

> expression analysis is useful, inter alia, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;
>
> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;
>
> antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;
>
> failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and
>
> failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

Appellants file herewith:

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");

2. the Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Bedilion Declaration");

3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and

4. Seven (7) references published before or shortly after the November 15, 1996 filing date of the priority Bandman '903 application,:

a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995) (Reference No. 1)

b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995) (Reference No. 2)

c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (Reference No. 3)

d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (Reference No. 4)

e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996) (Reference No. 5)

f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (Reference No. 6)

g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997) (Reference No. 7)

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1996 would have understood that any expressed polypeptide or expressed polynucleotide is useful for a number of gene and protein expression monitoring applications, e.g., in 2-D PAGE technologies or cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

> It is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state. [Rockett Declaration, ¶ 11.]
>
> Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s. [Rockett Declaration, ¶ 14.]
>
> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology. [Rockett Declaration, ¶ 18.][1]

In his Declaration, Dr. Bedilion explains why a person of skill in the art in 1996 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1996 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7).

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 9, 1995, describes an expression profiling platform, the "genome reporter matrix," which is based upon the measurement of protein expression levels. The '588 patent further describes use of nucleic acid microarrays to measure

[1] ."Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

transcript expression levels, making clear that the utility of comparing multidimensional expression data sets equally applies to protein expression data and transcript expression data.

The '588 patent speaks clearly to the usefulness of such expression analyses, particularly but not exclusively protein expression profiling, in drug development and toxicology, particularly pointing out that a protein's failure to change in expression level is a useful result. Thus, with emphasis added,

> [The invention provides] methods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug. [abstract]
>
> The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism. [column 1]
>
> The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix. [column 2]
>
> Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects. [columns 2-3]
>
> Furthermore, it is not necessary to know the identity of any of the responding genes. [column 3]
>
> [A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical. [column 4]

The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters. [column 4]

A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included. [columns 6-7]

In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug. [columns 7-8]

In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile. [column 8]

> The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses. [column 8]
>
> Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli. [column 9]
>
> The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s). [column 9]

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of nucleic acid microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]
>
> The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]
>
> The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof. [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term "disease" or "disease state" refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term "solid support" refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By "EST" or "Expressed Sequence Tag" is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are

used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Applicants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression patterns, or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

[The invention provides a] method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens. [abstract]

[W]e see each individual gene product as a "pixel" of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual "pixels" of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]

The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]

High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]

The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]

The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]

The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [i.e., the results yield analogous data to microarrays] [page 8]

Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]

In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as "gene transcript image analysis" or "gene transcript frequency analysis". The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models. [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]

[T]his research tool provides a way to get new drugs to the public faster and more economically. [page 36]

In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]

[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), filed on October 11, 1996 and published on April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the WO 97/13877 publication describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> [T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates. [Field of the invention]
>
> An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems. [page 3]
>
> Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals. [page 3]
>
> The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity. [page 3]
>
> As used herein, the terms "gene expression profile," and "gene expression pattern" which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand. [page 7]
>
> The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . [page 7]

In light of this and other evidence of the state of the art, one of ordinary skill in the toxicology arts would conclude that "[i]t is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological

function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology." (Rockett Declaration, ¶ 18.)

C. Responses to Specific Arguments by Examiner

1. Use of the claimed polypeptide in toxicology testing

The Examiner argues, on page 17 of the Examiner's Answer, that Appellants' arguments and the Furness Declaration are "not found to be persuasive" because "[s]ince any polypeptide can be used in 2-D PAGE gels or western blots, such a use is not specific to the claimed polypeptide" and "since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polypeptide, the results of protein expression monitoring assays would be meaningless without further research" and thus the utility is "not substantial."

The Examiner's arguments amount to nothing more than the Examiner's disagreement with the Furness Declaration and the Appellants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Appellants' expert. The Examiner must accept the Appellants' assertions to be true. The Examiner is, moreover, wrong on the facts because the Furness Declaration demonstrates how one of skill in the art, reading the specification at the time the Bandman '903 application was filed (November 15, 1996), would have understood that specification to disclose the use of the claimed polypeptide in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the Furness Declaration at, e.g., ¶¶ 9-13).

For example, detecting the expression of the SEQ ID NO:1 polypeptide is a method of testing the toxicology of drug candidates during the drug development process. Mr. Furness in his Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets." (Furness Declaration ¶ 10.) Thus, if the expression of a particular polypeptide is affected in any way by exposure to a test compound, and if that particular polypeptide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polypeptide whose expression is being monitored.

However, the Examiner continues to view the utility in toxicology testing of the claimed polypeptide as requiring knowledge of either the biological function or disease association of the claimed polypeptide. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polypeptide. The Examiner has refused to consider that the claimed polypeptide is useful for measuring the toxicity of drug candidates which are targeted not to the claimed polypeptide, but to other polypeptides. This utility of the claimed polypeptide does not require any knowledge of the biological function or disease association of the SEQ ID NO:1 polypeptide and is a specific, substantial and credible utility.

2. Discussion of toxicology testing in the Specification

The Examiner alleges that "[t]he particulars of toxicology testing with the claimed polypeptides are not disclosed in the instant specification." (Examiner's Answer, page 21) Well-established utilities, such as toxicology testing by the use of two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) maps, need not be explicitly disclosed in a patent application. Furthermore, the Examiner's position amounts to nothing more than the Examiner's disagreement with the Furness Declaration (which purports therefore to substitute the Examiner's judgment for that of Appellants' expert) and Appellants' assertions about the knowledge of a person of ordinary skill. The Examiner must accept Appellants' assertions to be true. The Examiner's Answer fails to address the disclosure in the instant specification on gene and protein expression monitoring applications, as discussed below.

Support for the utility of the claimed polypeptide in toxicology testing, as well as for utility in drug screening, may be found in the specification. For example, "protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies" may be used" for the detection and/or quantification of nucleic acid or protein." (Bandman '903 application, e.g., at page 22, lines 25-27.)

Further:

> A variety of protocols including ELISA, RIA, and FACS for measuring HSEBP are known in the art and provide a basis for diagnosing altered or abnormal levels of HSEBP expression. Normal or standard values for HSEBP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to HSEBP under conditions suitable for complex formation The amount of standard complex formation may be quantified by various methods, but preferably by photometric, means. Quantities of HSEBP expressed in subject, control and disease, samples

> from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease. (Bandman '903 application at page 33, line 34 through page 34, line 12.)

Moreover, the priority Bandman '903 application discloses that "HSEBP, its catalytic or immunogenic fragments or oligopeptides thereof, can be used for screening libraries of compounds in any of a variety of drug screening techniques" and that " one may use competitive drug screening assays in which neutralizing antibodies capable of binding HSEBP specifically compete with a test compound for binding HSEBP." (Bandman "903 application, page 38, lines 6-8 and 21-23.)

3. Biological significance is irrelevant to utility

The Examiner's Answer argues that the use of the claimed polypeptide in expression profiling is not adequate to provide patentable utility for the claimed polypeptide as "[t]he first requirement is that one must know the biological significance of the polypeptide(s) which is (are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polypeptide expressed should be increased or decreased or even what significance could be attributed to such changes in expression profiles." (Examiner's Answer, page 22.)

Appellants have demonstrated a utility for the claimed polypeptide irrespective of whether or not a person would wish to perform additional experimentation on biological significance as another utility. The fact that additional experimentation could be performed to determine the "biological significance" of the claimed polypeptide does not preclude, and is in fact irrelevant to, the actual utility of the invention.

For example, see the Rockett Declaration:

> It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology. [Rockett Declaration, ¶ 18.]

4. Structural similarity is predictive of functional similarity[2]

The Examiner's Answer alleges that "*among related polypeptides* in the selenium-binding families, structural similarity is not predictive of functional similarity." (Examiner's Answer, page 30, italics in original.) Appellants note that none of the papers cited by the Examiner (Tischer et al., Kopchick et al., Bowie et al., Burgess et al., Lazar et al., Bork (2000), Scott et al., Benjamin et al., Vukicevic et al., Massague, Pilbeam et al., Skolnick et al., Doerks et al., Smith et al., Brenner (1999), and Bork et al. (1996)) appear to be directed to selenium-binding proteins.

Furthermore, as noted by Appellants in the Appeal Brief (but not addressed by the Examiner in the Examiner's Answer), it is well known in the art that sequence similarity (measured by statistical scores as in Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998); Reference No. 8. previously submitted also with the Response filed December 17, 2002) is predictive of similarity in functional activity. H. Hegyi and M. Gerstein ("The Relationship between Protein Structure and Function: a Comprehensive Survey with Application to the Yeast Genome," J. Mol. Biol. (1999) 288:147-164; Reference No. 9; previously submitted also with the Appeal Brief) state that "the proportion of homologues with different functions is around 10%. This shows that there is a low chance that a single-domain protein, highly homologous to a known enzyme, has a different function." (Hegyi and Gerstein, Reference No.9, page 159, column 1, emphasis added.) Furthermore, Hegyi and Gerstein in a second journal article (H. Hegyi and M. Gerstein, "Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins," Genome Research (2001) 11: 1632-1640; Reference No. 10; previously submitted also with the Appeal Brief) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3." (Hegyi and Gerstein, Reference No. 10, page 1635.) Hegyi and

[2] The Examiner's Answer contains statements in at least four locations over three pages that appear to reference patent applications other than the instant application. The Examiner states that "Appellant urges that the teachings of Bowie et al. are counter to the outstanding rejections and supportive of the asserted utilities for **NDB17**." (Examiner's Answer, page 28, emphasis added.) The Examiner also alleges that "the disclosed **NDB17** has biological activities similar to known selenium binding family is not credible in the absence of supporting evidence." (Examiner's Answer, page 30, emphasis added.) The Examiner states that "Appellant submits that the amino acid differences between the polypeptides encoded by the **claimed polynucleotides** and known **growth factor proteins** are likely to occur at positions of minimal functional importance." (Examiner's Answer, page 29, emphasis added.) The Examiner states that "Appellant concludes that one of ordinary skill in the art would view the level of conservation between the claimed polypeptide encoding **NADH dehydogenase subunits** is indicative of a common function." (Examiner's Answer, page 29, emphasis added.) Appellants note that the instant Specification does not recite "NDB17" or "growth factor proteins" or "NADH dehydrogenase subunits" and that the appealed claims are directed to polypeptides. Appellants therefore assume that the Examiner used the terms "NDB17," "growth factor proteins," "claimed polynucleotides," and "NADH dehydrogenase subunits" inadvertently.

Gerstein also concluded that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "[t]he probability that the functions are the same in this case was 91%." (Hegyi and Gerstein, Reference No. 10, page 1636.) Hegyi and Gerstein (Reference No. 10, page 1632) further note that

> Wilson et al. (2000) compared a large number of protein domains to one another in a pair-wise fashion with respect to similarities in sequence, structure, and function. Using a hybrid functional classification scheme merging the ENZYME and FlyBase systems (Gelbart et al. 1997; Bairoch 2000), they found that precise function is not conserved below 30–40% identity, although the broad functional class is usually preserved for sequence identities as low as 20–25%, given that the sequences have the same fold. Their survey also reinforced the previously established general exponential relationship between structural and sequence similarity (Chothia and Lesk 1986).

Therefore, it is well known in the art that sequence similarity can be used to reliably predict functional similarity. HSEBP shares 96% sequence identity with human fetal heart selenium-binding protein (G1374792; SEQ ID NO:3), 86% sequence identity with mouse liver selenium-binding protein (G227630; SEQ ID NO:4), and 88% sequence identity with mouse liver acetaminophen-binding protein (G298710; SEQ ID NO:5), well above the thresholds described in the Hegyi and Gerstein Genome Research article (Reference No. 10) cited above. Therefore, there is a reasonable probability that the utility of human fetal heart selenium-binding protein, mouse liver selenium-binding protein, and mouse liver acetaminophen-binding protein can be imputed to the SEQ ID NO:1 polypeptide.

In addition, as discussed *supra*, "biological function" or 'biological significance" is irrelevant to the utility of the claimed naturally occurring polypeptide in toxicology testing.

5. Irrelevance of differential expression or disease association to utility in toxicology testing

The Examiner's Answer argues e.g., on pages 4, 8, 13, 14, 15, 17, 18, 19, 20, 22, 25, 26, 27, and 28 of the Examiner's Answer that the specification does not disclose whether the claimed polypeptide is differentially expressed in different tissues or associated with any disease. This is irrelevant. Appellants need not demonstrate whether the claimed polypeptide is differentially expressed or associated with any disease, only whether the claimed polypeptide is useful. The

claimed polypeptide is useful whether or not the claimed polypeptide is differentially expressed in any tissues or is associated with any disease.

The claimed polypeptide can be used for toxicology testing in drug discovery without any knowledge of differential expression or disease association of the claimed polypeptide. Monitoring the expression of the claimed polypeptide gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polypeptide, regardless of the differential expression or disease association of the claimed polypeptide. The claimed polypeptide is useful for measuring the toxicity of drug candidates specifically targeted to other polypeptides, regardless of any possible utility for measuring the properties of the claimed polypeptide. (See also Rockett Declaration, ¶¶ 14 and 18, and Iyer Declaration, ¶ 9.)

Appellants note that monitoring the expression of the claimed polypeptide is a method of testing the toxicology of drug candidates during the drug development process. If the expression of a particular polypeptide is affected in any way by exposure to a test compound, and if that particular polypeptide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects that may limit its usefulness as a specific drug. Toxicology testing using expression profiling using 2-D PAGE reduces time needed for drug development by weeding out compounds which are not specific to the drug target. Learning this from an array in a protein expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polypeptide whose expression is being monitored.

As an example, any actin gene or histone gene expressed in humans can be used in a specific and substantial toxicology test in drug development. As the Examiner recognizes, "actin and histone genes are . . . constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient." (Examiner's Answer, page 18.). An actin gene or histone gene may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed actin gene or histone gene is surely an excellent subject for toxicology studies when developing drugs targeted to other genes. A drug candidate which alters expression of an actin gene or histone gene is toxic because disruption of such a constitutively expressed gene would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene, measuring the expression of an actin gene or histone gene is a

good measure of the toxicity of that candidate, particularly in in vitro cellular assays at an early stage of drug development. The utility of any particular human-expressed actin gene or histone gene in toxicology testing is specific and substantial because a toxicology test using that actin gene or histone gene cannot be replaced by a toxicology test using a different gene, including any other actin gene or histone gene. This specific and substantial utility requires no knowledge of the biological function or disease association of the actin gene or histone gene.

6. Utility of all expressed polypeptides in toxicology testing

The Examiner argues that use of the claimed polypeptide in toxicology testing is not acceptable because "this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA" and that "such a utility is not specific." (Examiner's Answer, page 21.) The Examiner does not point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of expressed polypeptides can be so used, then they all have utility. The issue is, once again, whether the claimed polypeptide has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of well-established" utilities PRESUPPOSES that many different inventions can have the exact same utility (if the Examiner's argument were correct, there could never be a well-established utility, because you could always find a generic group with the same utility!).

It is true that just about any expressed polypeptide will have use as a toxicology control, but Appellants need not argue this for the purposes of this case. Appellants argue only that the claimed polypeptide could be so used, and has provided the declarations of Furness, Rockett, Bedilion, and Iyer to back this up. The point is not whether or not the claimed polypeptide is, in any given toxicology test, differentially expressed. The point is that the claimed polypeptide provides a useful measuring stick regardless of whether there is or is not differential expression. That makes the invention useful today, in the real-world, for real purposes.

7. Commercial Success of the Incyte's Databases as Evidence of Utility

On pages 23-24 of the Examiner's Answer, the Examiner criticizes Appellants' citation of the commercial success of Incyte's databases as evidence of the commercial value of the contained information on the claimed polypeptide. The Examiner argues that "many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable" including "silly fads such as pet rocks, but also. . . serious scientific products like

orphan receptors." (Examiner's Answer, page 24.) Appellants note that there are at least two U.S. Patents claiming orphan receptors (U.S. Patent Nos. 5,958,710 and 6,277,976).

8. The Examiner's reliance on Brenner v. Manson is misplaced

This is not a case in which biological function or disease association or differential expression is necessary to provide a link between the claimed invention on one hand, and a compound of known utility on the other. Given that the claimed invention is disclosed in the Bandman '903 application to be useful as a tool in a number of gene and protein expression monitoring applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, the precise biological function or disease association or differential expression of the claimed polypeptide is superfluous information for the purposes of establishing utility.

That the claimed invention already has a disclosed use as a tool in then available technology (such as expression profiling using 2-D PAGE) distinguishes it from those few claimed inventions found not to have utility. In each of those cases, unlike this one, the person of ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Examiner's unsupported statement that one of those cases, Brenner v. Manson, 383 U.S. 519, 532, 534-35 (1966), is somehow analogous to this case is plainly incorrect. (Examiner's Answer, pages 19 and 23.)

Brenner concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In Brenner, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in Brenner produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In Brenner, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the claimed SEQ ID NO:1 polypeptide is an expressed polypeptide that was disclosed in the priority Bandman '903 application to be useful for many

known applications involving gene and protein expression monitoring analysis. Its utility is not a matter of guesswork. It is not a random DNA or protein sequence that might or might not be useful as a scientific tool. Unlike the steroid in Brenner, the utility of the invention claimed here is not grounded upon being structurally analogous to a molecule which belongs to a class of molecules containing a significant number of useless compositions.

And, the utilities disclosed in the application are for purposes other than just studying the claimed invention itself, Brenner, 383 U.S. at 535, i.e., for other (non self-referential) uses such as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug. Indeed, in view of the Furness Declaration (at, e.g., ¶ 12), the evidence shows that persons skilled in the art on November 15, 1996, who read the Bandman '903 application, would have believed the claimed polypeptide to be so useful that they would request specifically that any 2-D PAGE map that was being used in connection with developing new drugs for the treatment of cancer utilize the SEQ ID NO:1 polypeptide sequence.

Accordingly, in this case, biological function or disease association or differential expression is in fact superfluous information for the purposes of demonstrating utility. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function, as the Furness Declaration, Bedilion Declaration, Rockett Declaration, and the Iyer Declaration, and other evidence presented by the Appellants demonstrates. Given that the claimed invention has disclosed and well-established utilities, the Appellants need not demonstrate utility by imputation or by showing disease association or differential expression.

In the end, the Examiner has failed to recognize that new technologies, such as those involving the use of 2-D PAGE to conduct protein expression analyses, have made useful biological molecules that might not otherwise have been useful in the past. See Brenner, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polypeptide could be usefully employed without further research. It has created a need for new tools, such as the claimed polypeptide, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and real-world benefits to the public by enabling faster, cheaper and safer drug discovery processes. The Examiner is obliged, by law, to recognize this reality.

II. ENABLEMENT REJECTION OF CLAIM 1, 2, 13, AND 14

The rejection set forth in the Examiner's Answer is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Examiner's Answer, pages 9 and 31). To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

For at least the above reasons, reversal of the enablement rejection is requested.

III. WRITTEN DESCRIPTION REJECTION OF CLAIMS 1, 2, 13, and 14

A. Nowhere in the Examiner's Answer does the Examiner offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Appellants were in possession of the claimed polypeptide comprising a naturally-occurring amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1, the claimed biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and the claimed immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

The Examiner alleges that the "specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides," that "[t]here is no description of the conserved regions which are critical to the structure and function of the genus claimed," and that "[s]tructural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure." (Examiner's Answer, pages 11-12.) The Examiner further alleges that "[t]he disclosure fails to describe the common attributes or characteristics that identify the members of the genus" and that "[t]he genus is highly variant." (Examiner's Answer, page 12.)

The Examiner's position is clearly contrary to the USPTO's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of**

> **the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described** in the specification, then the adequate description requirement is met. (citations omitted, emphasis added)

Here, there simply is no requirement that the claims recite particular variant polypeptide sequences, or particular biologically-active or immunogenic fragments, because the claims already provide sufficient structural and functional definition of the claimed subject matter. That is, the polypeptide variants and fragments are defined in terms of SEQ ID NO:1 ("An isolated polypeptide selected from the group consisting of: a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, b) a polypeptide comprising a naturally-occurring amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1, c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1."

Because the polypeptide variants and fragments are defined in terms of SEQ ID NO:1, the precise chemical structure of every polypeptide variant and fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention. Appellants further submit that given the polypeptide sequence of SEQ ID NO:1, it would be redundant to list specific fragments. The structure of SEQ ID NO:1 provides the blueprint for all fragments thereof. Listing all possible fragments of SEQ ID NO:1 is, thus, a superfluous exercise which would needlessly clutter the Specification. Accordingly, the Specification provides an adequate written description of the recited polypeptides.

B. The Examiner alleges that "it is not true that one could find in nature any and all possible changes within a given gene, and the specification has described not a single variant of SEQ ID NO:1. . . There is not a single sequence disclosed that is obtained from another biological species." (Examiner's Answer, page 33.) Appellants are not claiming "any and all possible changes within a given gene." Appellants claim a polypeptide comprising a naturally-occurring amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1.

C. The Examiner questions the truth of Appellants' statement on page 31 of the Appeal Brief that "[g]iven SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 at least 96% identical to SEQ ID NO:1." The

Examiner alleges that "[o]ne could certainly determine whether a protein that one had obtained from nature were 96% identical to SEQ ID NO:1, but that same person, handed a protein a test tube, would have no way of determining whether that protein were 'naturally occurring.'" (Examiner's Answer, page 33.)

Appellants note that sequence information is not provided in a vacuum. Identification of the source of the sequence will typically allow one to determine if it is naturally-occurring. Also, attempted deceit to hide the source will not preclude infringement.

The Examiner further alleges that the Specification does not provide "the relation of structure to function." (Examiner's Answer, page 12.) However, functional limitations are not necessary as the structural and source limitations are sufficient to describe the claimed polypeptide variants and, in any case, "biological function" is irrelevant to the use of the claimed polypeptide variants in toxicology testing.

D. The Examiner contends that "[w]hile 96% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function." (Examiner's Answer, page 35.) The Examiner further alleged that "[t]here is no description about the function of the gene nor the protein encoded thereby, such as would allow one of skill to predict what portions of the disclosed sequence would be expected to be conserved." (Examiner's Answer, page 32.) As the claimed variants are not described by their having the same "function" as SEQ ID NO:1, the Examiner's arguments are not relevant to the written description issue.

Nevertheless, Appellants note that it is well known in the art that sequence similarity is predictive of similarity in functional activity. Hegyi and Gerstein (supra; Reference No. 10) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3." (Reference No. 10, page 1635.) Hegyi and Gerstein also concluded that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "[t]he probability that the functions are the same in this case was 91%." (Reference No. 10, page 1636.) Hegyi and Gerstein (Reference No. 10, page 1632) further note that

> Wilson et al. (2000) compared a large number of protein domains to one another in a pair-wise fashion with respect to similarities in sequence, structure, and function. Using a hybrid functional classification scheme merging the ENZYME and FlyBase systems (Gelbart et al. 1997; Bairoch 2000), they found

> that precise function is not conserved below 30–40% identity, although the broad functional class is usually preserved for sequence identities as low as 20–25%, given that the sequences have the same fold. Their survey also reinforced the previously established general exponential relationship between structural and sequence similarity (Chothia and Lesk 1986).

The claimed polypeptides share more than 96% sequence identity with the SEQ ID NO:1 polypeptide, well above the thresholds described in the Hegyi and Gerstein Genome Research article (Reference No.10) cited above. Therefore, there is a reasonable probability that the SEQ ID NO:1polypeptide variants would have the same function as the SEQ ID NO:1 polypeptide.

E. The Examiner further states that "VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but nor for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells, though the two are closely related." (Examiner's Answer, page 35.) Appellants submit that these are not "opposite" biological activities, as the Examiner would have it. As the Examiner recognizes, both VEGF and PDGF are mitogenic for vascular cells. Although the specific vascular cells for which VEGF and PDGF are mitogenic are different, these two growth factor proteins nevertheless have very similar biological activities.

For at least the above reasons, reversal of the written description rejection is requested.

CONCLUSION

For all the foregoing reasons and the reasons stated in Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This brief is enclosed in triplicate.

Respectfully submitted,
INCYTE CORPORATION

Date: January 5, 2004

Susan K. Sather
Reg. No. 44,316
Direct Dial Telephone: (650) 845-4646

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Enclosures:
Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with attached Exhibits A-Q

Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E

Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132

Ten references:
1. PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995)
2. PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995)
3. M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995)
4. PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995)
5. U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996)
6. R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150-2155 (March 1997)
7. PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997)

8. S. E. Brenner et al., Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998)
9. H. Hegyi and M. Gerstein, The relationship between protein structure and function: a comprehensive survey with application to the yeast genome, J. Mol. Biol. 288:147-164 (1999)
10. H. Hegyi and M. Gerstein, Annotation transfer for genomics: measuring functional divergence in multi-domain proteins, Genome Research 11: 1632-1640 (2001)